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The Patent Office
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16 APR 2004
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Request for grant of a patent

The Patent Office
Cardiff Road
Newport
South Wales NP10 8QQ

1. Your reference
1910001/AM

2. Patent Application Number
0408535.3
16 APR 2004

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

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Patents ADP number *(if known)* 08606295002

If the applicant is a corporate body, give the country/state of its incorporation — Country: **England** State:

4. Title of the invention

INSOLUBLE DRUGS

5. Name of agent
"Address for Service" in the United Kingdom to which all correspondence should be sent

Beresford & Co
16 High Holborn
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Patents ADP number
00001826001

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications filed in the last 12 months.

Country	Priority application number	Date of filing

Patents Form 1/77

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute.

Number of earlier application | Date of filing

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Yes

9. Enter the number of sheets for any of the following items you are filing with this form.

Continuation sheets of this form	
Description	2
Claim(s)	1
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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents form 7/77)*	**1 + 2 copies**
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Request for Substantive Examination *(Patents Form 10/77)*	
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11. I/We request the grant of a patent on the basis of this application

Signature Beresford & Co — Date 16 April 2004

BERESFORD & Co

12. Name and daytime telephone number of person to contact in the United Kingdom

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insoluble drugs.

Introduction

Many drugs administered for various pharmacological effects are limited or completely insoluble in aqueous solutions. The human or animal body can be considered to be made up of a number of compartments into which the drug permeates dependent upon issues *inter alia* perfusion, partition coefficient of the drug in the tissue in each compartment, etc. Additionally, certain drugs are known to undergo non-specific binding particularly to plasma proteins. This creates difficulties when seeking to administer the appropriate therapeutic dose as time constants; ultimate concentrations in various tissues etc are difficult to estimate.

This is particularly the case with but not limited to lipophilic aqueously insoluble anaesthetics agents such as 2:6diisoproylphenol (propofol) where tight control of anaesthesia is required.

Concept

It is proposed that the concentration of propofol be measured directly in blood during and after drug administration.

This can be doe by using the physio-chemcial properties of the drug to enable detection.

Firstly, propofol is known to fluoresce and this can be used as a method of quantification when measured optically by a fibre optic, optically coupled chip or by measurement non-invasively by transmitted or reflected light.

Further purification and concentration of the drug can be achieved *in situ* by encapsulating or covering the sensing elements in a material, solid or liquid, into which propofol preferentially partitions over the tissue it is in. Conceptually, this should be relatively easy to achieve due to the highly lipophilic nature of the drug.

Also, specific recognition molecules may be found or more likely designed and fabricated such as molecularly imprinted polymers that have a high binding affinity for the analyte of interest, i.e., preferentially bind the molecule of interest such as propofol.

The binding of the analyte molecule can be a direct concentration step allowing detection by a number of means, optical, electrochemical, conductimetric, gravimetric or spectroscopic. It is also possible that the specific binding event causes a physio-chemical change detectable by a standard sensor transduction technique such as, but not limited to, potentiometry, amperometry, conductimetry, and spectroscopy, chromatography, capacitance and micro-balances, resonant sensors, thermal methods and calorimetry.

Further information regarding the status of the analytes distribution through the different tissues is the possibly of measuring the relative concentrations in different body compartments. For example the pharmacokinetics of propofol can be described by a simple three-compartment linear model with compartments representing the plasma, rapidly equilibrating tissues, and slowly equilibrating tissues. Thus, it is possible to measure the anaesthetic levels in the plasma and one or more of the other compartments for example the slowly equilibrating tissue subcutaneously. The ratios can be calculated that will provide greater detail of the distribution of the drug. With a clear understanding of the pharmacokinetics the slowly equilibrating tissues alone may be able to be measured in tissues such as the earlobe or subcutaneous tissue by invasive minimally invasive or non-invasive techniques. In conjunction with the infusion rate data and patent demographics these data could be used to accurately estimate overall drug distribution.

In turn data derived in this fashion could be use to provide the input for closed-loop drug administration when coupled with the appropriate administration device and control algorthythm.

Particularly attractive in this context is the use of micro-needles to sample fluids such as but not limited to interstitial fluid, intracellular fluid, blood and plasma in a minimally invasive manner. Also micro-needles could be used as wave guides or "light wells" to gain optical access to and or from the skin obviating some of the absorption form the upper layers of the stratum corneum and epidermis. Additionally, micro-needle devices could be introduced into the skin to provide scattering centres to improve optical signal.

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